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B.C.G. AND VOLE BACILLUS VACCINES IN THE PREVENTION OF TUBERCULOSIS IN ADOLESCENTS

FIRST (PROGRESS) REPORT TO THE MEDICAL RESEARCH COUNCIL BY THEIR TUBERCULOSIS VACCINES CLINICAL TRIALS COMMITTEE*

It is now more than thirty years since a live vaccine containing B.C.G. (bacille Calmette-Guérin) was first used in man. In the interval B.C.G. vaccination has come to be accepted in many countries as an effective method of preventing progressive tuberculosis, and it has been particularly widely used since 1945. It has, however, been adopted to only a limited extent in Great Britain. Despite the many millions of vaccinations which have been undertaken, there is still disagreement on the value of the vaccine as a preventive measure. In particular, there has been no adequate study of the contribution which it might make to the control of tuberculosis in an industrial community, such as that in Great Britain, with well-developed health services and with relatively low tuberculosis incidence and mortality.

In 1937 Wells discovered the mycobacterium of vole tuberculosis, and later explored the use of a live vaccine containing it. Vole bacillus vaccine has since been used in a few countries, but on a very small scale compared with B.C.G. vaccine. Its value as a preventive measure has also not been fully assessed.

In July, 1949, the Medical Research Council, aware that a clinical trial of these two vaccines was needed to provide essential information, appointed a Tuberculosis Vaccines Clinical Trials Committee to plan and direct an appropriate investigation. The following is the first report of this trial, which is still in progress. It presents preliminary findings up to the time at which each participant had been in the trial for two and a half years, with some supplementary incomplete information up to four years.

The work described was carried out by the Council's Tuberculosis Research Unit, with the assistance of many other statutory and voluntary organizations, whose help is acknowledged at the end of the report. The team operating in the London area was directed first by Dr. W. Pointon Dick and later by Dr. T. M. Pollock, that in the Birmingham area by Dr. J. P. W. Hughes and later by Dr. D. N. Mitchell, and that in the Manchester area by Dr. G. G. Lindsay and later by Dr. S. Keidan. The trial was co-ordinated by the late Dr. Marc Daniels and then by Dr. Pollock. Throughout the planning and execution of the trial there has been close co-operation with the Council's Statistical Research Unit, and Dr. Ian Sutherland of that unit has taken a major part in it. Dr. Pollock and Dr. Sutherland have analysed the results and prepared the present report. Assessments of the cases of tuberculosis were made by Dr. V. H. Springett; a few supplementary assessments of non-pulmonary disease were made by Mr. J. A. Cholmeley.

Examinations of cultures from cases of tuberculosis in B.C.G.-vaccinated children were undertaken by Colonel H. J. Bensted and Dr. H. D. Holt, and in vole-bacillus-vaccinated children by Dr. A. Q. Wells. Histological specimens were assessed by Dr. R. J. W. Rees. Part-time assistance to the physicians directing the teams was given by Dr. Christine Miller, and also by Dr. E. C. Fear, Dr. W. L. Gordon, and Dr. Phyllis A. Lavelle. Advice on radiological procedures was given by Dr. A. J. Eley, who also, with Dr. L. A. McDowell and Dr. J. Rimington, made independent duplicate readings of the routine chest radiographs taken by the teams. Advice on the classification of primary tuberculosis in adolescents was given by Dr. Margaret MacPherson. The planning of the trial was assisted by preliminary data assembled by Dr. Pointon Dick, and by the findings of the National Tuberculin Survey, 1949–50 (Medical Research Council, 1952).

I. PLAN AND CONDUCT OF THE TRIAL

To assess the contribution of each of the two vaccines to the control of tuberculosis in the community, it was desirable to study their effects under ordinary conditions of life, and not in groups with a special risk of exposure to the disease. The Committee decided that it was of importance to investigate the degree and the duration of protection afforded by each vaccine in adolescence, since the notification rate and mortality from tuberculosis in Great Britain begin to rise at about the age of 15 years from their low levels in childhood. For the same reason any benefit from vaccination would be most readily detected in adolescence. It was also recognized that the incidence of tuberculosis in the vaccinated groups must be compared with that in a similar but unvaccinated group, and that this comparison would not be valid unless those suitable for vaccination were assigned at random to the vaccinated and unvaccinated groups. Moreover, the adolescents would have to be followed up intensively for a period of several years at least, and a variety of methods, including regular radiographic examinations, would be required to ensure that few, if any, of the cases of tuberculosis which arose would escape detection. Finally, large numbers of

*Members of the Committee: Dr. P. D'Arcy Hart (chairman), Sir John Charles, Professor R. Cruickshank, Dr. Marc Daniels (secretary until his death in 1953), Dr. W. Pointon Dick (resigned in 1951), Dr. J. E. Geddes, Professor A. Bradford Hill, Sir Wilson Jameson, Dr. V. H. Springett, Dr. Ian Sutherland, Dr. A. Q. Wells, Dr. G. S. Wilson, Dr. T. M. Pollock (secretary).

young people had to be included in the trial, partly because a substantial proportion would give a positive reaction to tuberculin and so be ineligible for vaccination, and partly because the total incidence of tuberculosis would not be large, and it was important to be able to detect even minor degrees of protection due to the vaccines.

Arising out of these considerations, the general plan of the trial was to include more than 50,000 boys and girls during their final year at secondary modern schools, when nearly all of them were aged between 14½ and 15 years. (A description of these schools was given by the Ministry of Education in 1947; in 1953 they were attended by half the child population of England and Wales aged between 14 and 15 years—Ministry of Education, 1954.) Children giving a negative reaction to tuberculin were divided by an effectively random process into three groups; those in one group were not vaccinated, those in another received B.C.G. vaccine, and those in the third group received vole bacillus vaccine. The children with a positive reaction to tuberculin, as well as those in the unvaccinated and the two vaccinated groups, have been questioned and examined at intervals since they left school, with the aim of discovering all the cases of tuberculosis which occurred. A more detailed account of the organization of the trial follows.

The Intake

To obtain the large number of volunteers required, and to facilitate their periodic re-examination, it was necessary to carry out the investigation in large and densely populated areas. Suitable districts were therefore selected in or near North London, Birmingham, and Manchester (see Acknowledgments). The conduct of the trial in each of these three areas has been the responsibility of a special team of the Tuberculosis Research Unit, headed by a physician, and equipped with a mobile van for miniature radiography (lent by the Ministry of Health). The trial has been co-ordinated centrally at the unit's headquarters, Hampstead, London; techniques were standardized and frequent staff meetings have been held. In each area the support and assistance of the county borough, county and local medical officers of health, and the school medical officers, were enlisted, and approaches were made, through the education authorities, to the head teachers of the secondary modern schools in the chosen districts.

The intake of volunteers in the London area lasted from the autumn term, 1950, to the spring term, 1952, and in the Birmingham and Manchester areas from the spring term, 1951, to the autumn term, 1952. During the intake the team visited each of the chosen districts once in each school term. Before the visit a leaflet was distributed to all the children who were in their penultimate term at school, explaining the scheme and inviting them to participate, subject to the written consent of their parents. Approximately 60% of those approached agreed to take part and attended for a first examination. Nearly all the children were aged between 14½ and 15 years and were born in 1936, 1937, or 1938 (all were between 14 and 15½ years).

First Examination of Participants

The first examination took place at a convenient centre, which was usually one of the schools. In addition to personal information, details (supplied by the parents) of any history of tuberculosis in the immediate family, and of any recent contact with the disease, were noted on a record card bearing a printed serial number. Children known to have been in recent contact with a case of pulmonary tuberculosis at home were excluded from the trial because they were already eligible for B.C.G. vaccination under a scheme introduced by the Ministry of Health in 1949.

Each child was given the following standard examination:

(*a*) A 35-mm. radiograph of the chest was taken. Any child whose film was considered by the physician in charge of the team to show unusual radiographic appearances was recalled for a full-plate chest radiograph. Children found or suspected to have any form of tuberculosis (apart from calcification of primary type) at this first examination were excluded from the trial and referred to their local chest clinic.

(*b*) An intracutaneous tuberculin (Mantoux) test was made on the forearm with 3.3 tuberculin units (3 T.U.), using 0.1 ml. of 1/3,000 Old Tuberculin (international standard strength; a single batch of heat-concentrated synthetic medium tuberculin, prepared in June, 1950, by the Ministry of Agriculture, Fisheries and Food, Veterinary Laboratory, Weybridge, Surrey); the greatest diameter of palpable infiltration at the end of 72 hours was recorded in millimetres.

(*c*) If there was no infiltration, or if its diameter was less than 5 mm., the reaction to 3 T.U. was regarded as negative, and another intracutaneous test was made on the same forearm with 100 T.U., using 0.1 ml. of 1/100 Old Tuberculin; the greatest diameter of infiltration at the end of 72 hours was again recorded.

Children with no infiltration, or with a diameter of infiltration of less than 5 mm., at the second tuberculin test, were regarded as negative reactors to 100 T.U. and were eligible for vaccination.

Those who completed this first examination (and who were not excluded on other grounds) were regarded as having entered the trial on the date of the first radiographic examination and tuberculin test.

Vaccination Procedures

In the London area, vole bacillus vaccine was not used, and the children eligible for vaccination were allocated equally, according to the final digit of the serial number appearing on their record card, to an unvaccinated or a B.C.G.-vaccinated group. (The serial number had been given, it will be recalled, before it was known whether the child was eligible for vaccination.) A similar procedure applied for a short period early in 1952 in the Birmingham and Manchester areas, when no vole bacillus vaccine was being prepared. Apart from this short period, the children eligible for vaccination in the Birmingham and Manchester areas were divided equally into three groups: those due to receive no vaccine, B.C.G. vaccine, or vole bacillus vaccine. The division was again made according to the final digit of the serial number on the record card; it had been arranged that in these areas the numbers did not end in 0. There were, however, several temporary failures in the supply of vole bacillus vaccine, and in these circumstances the children due to receive vole bacillus vaccine were given B.C.G. vaccine instead. There were also very occasional temporary failures in the supply of B.C.G. vaccine to the Birmingham and Manchester teams, and vole bacillus vaccine was then used instead.

The B.C.G. vaccine (0.75 mg. of semi-dried weight bacilli per ml.) was freshly prepared in liquid form by the State Serum Institute, Copenhagen, and was supplied through the Central Public Health Laboratory, Colindale, London. Each batch was stored in a refrigerator and used within eight days of its receipt, and within fourteen days of the harvesting of the cultures. The dose was 0.1 ml., injected intracutaneously in the left deltoid region in the boys, and in the upper and outer part of the left thigh in the girls.

The vole bacillus vaccine (2 mg. of wet weight bacilli per ml.) was freshly prepared in liquid form by Mr. A. F. B. Standfast and Miss D. Card at the Lister Institute, Elstree, Herts; the strains were provided by Dr. A. Q. Wells. Each batch was stored in a refrigerator and used within eight days of its receipt, and within fourteen days of the harvesting of the cultures. Unfortunately neither the concentration of bacilli nor the strain used was satisfactory in the earlier batches

(see below). The vaccine was introduced into the skin by a multiple-puncture instrument with 40 needles, projecting 2 mm. on release. The sites used were as for B.C.G. vaccination.

Those due to be vaccinated were given the appropriate vaccine immediately after the result of the test with 100 T.U. had been read.

Second Examination of Participants

The children who entered the trial in 1950 and in 1951 in their penultimate term at school were re-examined in their final term, after an interval usually of three to five months, when the team again visited the district. The purpose of this examination was to observe the immediate effects of vaccination and to obtain a further chest radiograph. The examination consisted of (*a*) a 35-mm. chest radiograph for every child, and, if indicated, a full-plate radiograph; (*b*) tuberculin tests, as at the first examination, for all children except those who had given strongly positive reactions at the previous test—that is, except those who either had given positive reactions to 3 T.U. or had shown a diameter of infiltration of at least 10 mm. to 100 T.U.; (*c*) the measurement of each B.C.G. vaccination reaction, and the classification of each vole bacillus vaccination reaction; (*d*) the recording of local complications of vaccination.

No participant was vaccinated or revaccinated at this or any subsequent examination by the teams.

Some children entered the trial only when they were in their final term, and so could not be examined for a second time at school. In addition, none of the children who entered the trial in 1952 was given a full second examination at school because the mobile radiography vans were already required for the follow-up examinations of the children who had entered at the beginning of the intake. In the Birmingham and Manchester areas, however, it was possible to perform tuberculin tests on, and examine the vaccination reactions for, a sample of the children given each batch of vaccine during 1952.

Follow-up of Participants

Each participant was approached directly three times in the period of approximately fourteen months after leaving school.

(1) Approximately four months after the child had left school an inquiry form was sent by post, asking for details of any intercurrent illnesses, hospital or clinic visits, and of any contact with tuberculosis. Those who did not reply were sent a second, and sometimes a third, form.

(2) Approximately ten months after leaving school the participant was visited at home by a health visitor on the staff of the local medical officer of health. She made the same inquiries as those on the postal form, reminded the participants that the team would shortly be in the district again, and urged them to attend for examination.

(3) Approximately fourteen months, and usually between ten and eighteen months, after the participant had left school the team revisited the district and set up the mobile radiography van at a suitable centre. The participants, now nearly all in employment, were invited to an examination which consisted of (*a*) a 35-mm. chest radiograph, and, if indicated, a full-plate radiograph; since June, 1954, all the radiographs have been read separately by the team physician and by an independent observer; (*b*) tuberculin tests, as at the first examination; every participant, whatever the results of the tuberculin tests at the first examination, was expected to have these tests, but some who attended for the radiograph failed to complete them; the results of the tuberculin tests were read by the team physician before looking at the record card, so that he was unaware of the results of the previous tuberculin tests and of whether any vaccination had been performed; (*c*) the inspection and measurement of each B.C.G. vaccination reaction, and the inspection and classification of each vole bacillus vaccination reaction. Participants who did not attend this examination were invited to an extra and similar examination when the team next visited the district seven months later. As stated above, none of the participants was vaccinated or revaccinated at any follow-up examination.

The same cycle of inquiry and examination has been repeated in each subsequent fourteen-month period, starting with a postal inquiry four months after the team had visited the district. Small but increasing numbers of the entrants, however, have moved to other parts of the country as the trial has proceeded, and a few have emigrated. They have been sent postal inquiry forms annually and arrangements have been made, through local or national health authorities, for an annual home visit and an annual radiographic examination, including, if possible, tuberculin tests.

Unsparing efforts have thus been made to keep in frequent touch with every volunteer, and these approaches have been the principal means for the discovery of the cases of tuberculosis occurring among them. Information has also been continually made available to the teams from the tuberculosis notification lists of the local medical officers of health, and from the records of the chest clinics in the districts concerned. Cases of tuberculosis have thus been discovered both by the unit's periodic radiographic examinations and by the normal methods of the National Health Service.

The physicians in charge of the three teams were not responsible for the further investigation or treatment of any participant who had an abnormal radiograph; those who were found to have an abnormal radiograph at an examination by one of the teams were referred to their local chest clinic. With very few exceptions, however, every case of definite or suspected tuberculosis, whether discovered by the teams or by the National Health Service, was also examined in due course by one of the unit physicians; further details of the progress of the case were thenceforward obtained at six-monthly intervals.

To ensure that cases of tuberculosis were not missed, full records were kept not only for the definite cases but also for those in which tuberculosis was either suspected or considered to be even a possible diagnosis. The records were kept centrally so that the cases could eventually be assessed and classified by an independent assessor. Details were also obtained of all deaths, from whatever cause.

The records available for each case thus consisted of periodic radiographs, the results of the clinical examination by one of the unit physicians, the results of clinical examinations by other physicians, and the results of any bacteriological or pathological examinations. If bacteriological or pathological confirmation of the diagnosis had not been otherwise obtained, further examinations were arranged by the unit physicians. Histological specimens were assessed at the National Institute for Medical Research.

In cases of definite or suspected tuberculosis arising in B.C.G.-vaccinated participants, any cultures growing acid-fast bacilli were examined as a routine at the Central Public Health Laboratory, Colindale, London, where the type, pathogenicity, and, if necessary, drug sensitivity of the bacilli were determined. Particular attention was paid to the possibility that the infecting organism was B.C.G. itself. Similarly, cultures growing acid-fast bacilli from vole-bacillus-vaccinated participants were examined at the Sir William Dunn School of Pathology, Oxford.

II. PROGRESS OF THE TRIAL

Sample Analysis of the Records

Since the trial is still in progress, the record cards with the results of the periodic examinations of each participant are in continual use. An exact enumeration of the participants, and a full analysis of the extent to which contact with them has been maintained, is thus at present impracticable. For this first report representative samples of the record cards held by each team have been used to estimate the numbers of participants in each area and in each follow-up

group, the numbers excluded from the trial, the results of the tuberculin tests at the second examination at school, and the extent of contact with the participants after they left school. The cases of tuberculosis among the participants, on the other hand, have been completely enumerated, and not estimated from the samples.

For these samples, all the record cards with serial numbers ending in certain pairs of digits were located in the files and information was transcribed from them on to a specially designed analysis card. The choice of pairs of digits was effectively random, while at the same time they were approximately equally spaced in each cycle of one hundred numbers and were chosen so as to ensure the correct representation of the tuberculin-negative unvaccinated group and of the two vaccinated groups (which, as already described, were determined by the final digit of the serial number). A 4% sample of the London area records and 3% samples of the Birmingham and Manchester area records were drawn.

Number of Participants in the Trial

A total of approximately 61,400 children presented themselves for the first examination at school. The following groups of children were excluded both from participation in the trial and from the analysis of the results: (*a*) Those who were suffering from any form of definite or suspected tuberculosis (apart from calcification of primary type) at the time of the first examination, whether diagnosed on entry to the trial or not until later. (*b*) Those who were in known contact with a case of pulmonary tuberculosis at home, either at the time of the first examination or within the previous two years, whether this was discovered on entry to the trial or not until later.

Approximately 1,800 children were excluded on one or other of these grounds. In addition, some 2,500 children failed to complete the initial radiographic examination and tuberculin tests, and so could not participate.

A small number of children, about 400 in all, were excluded from the analysis for various reasons, such as having been given the wrong vaccine, having incorrectly been left unvaccinated, or having received an anti-tuberculosis vaccination prior to entering the trial. After these exclusions there remained approximately 56,700 participants in the analysis.

As a result of the tuberculin tests and vaccinations at the first examination, the children were automatically classified on entry to the trial into the following five groups, in which they remain for the purpose of the ensuing analysis, whatever the results of subsequent tuberculin tests:

Negative unvaccinated.—Negative to 100 T.U. on entry and left unvaccinated.

B.C.G. vaccinated.—Negative to 100 T.U. on entry and then given B.C.G. vaccine.

Vole bacillus vaccinated.—Negative to 100 T.U. on entry and then given vole bacillus vaccine.

Positive to 3 T.U.—Positive to 3 T.U. on entry and left unvaccinated.

Positive only to 100 T.U.—Negative to 3 T.U. and positive to 100 T.U. on entry, and left unvaccinated.

The numbers of participants from each area, according to their skin-test and vaccination group, are shown in Table I. The largest intake was in the Birmingham area, where 23,400 adolescents took part, followed by the Manchester area with 18,800 and the London area with 14,500. In the three areas combined, 22,600 of the children (40%) gave a positive tuberculin reaction on entry, 16,000 (28%) reacting to the weaker concentration of tuberculin (3 T.U.). Of the 34,100 children who were negative reactors to tuberculin, 13,300 were left unvaccinated, 14,100 were given B.C.G. vaccine, and 6,700 were given vole bacillus vaccine.

Plan of the Present Report

It will be recalled that some children in the Birmingham and Manchester areas entered the trial when both B.C.G. and vole bacillus vaccines were being given, that others (including all those in the London area) entered when B.C.G. vaccine only was being given, and that a small number (approximately 700) entered when vole bacillus vaccine only was available. Throughout the trial, however, and whatever vaccines were being given, the children with negative reactions to tuberculin on entry were allocated at random to the unvaccinated and vaccinated groups.

TABLE I.—*Total Number of Participants in the Trial (Estimates Based on Representative Samples)*

Skin-test and Vaccination Group*	Area			All Areas	
	London	Birmingham	Manchester	No. of Participants	Percentage of Total
Tuberculin negative, left unvaccinated	4,400	5,200	3,700	13,300	*23*
Tuberculin negative, B.C.G. vaccinated	4,400	5,600	4,100	14,100	*25*
Tuberculin negative, vole bacillus vaccinated	—	3,900	2,800	6,700	*12*
Tuberculin positive to 3 T.U.	3,800	6,100	6,100	16,000	*28*
Tuberculin positive to 100 T.U., but not to 3 T.U.	1,900	2,600	2,100	6,600	*12*
All groups	14,500	23,400	18,800	56,700	*100*

* The group was determined for each participant on entry to the trial. For full definitions of the groups, applicable to this and to all the other tables, see text.

A valid assessment of the value of B.C.G. vaccination must be based upon those children who were admitted *concurrently* to the negative unvaccinated, the B.C.G. vaccinated, and the two tuberculin-positive groups. The data are presented in this way in Section A of Tables II to IV. (The comparison includes all the children admitted to the trial in these four groups, except the small number who entered when vole bacillus vaccine only was available.)

Some, but not all, of the children included in this assessment of B.C.G. vaccine entered the trial concurrently with children given vole bacillus vaccine. The results for these children, concurrently admitted to the negative unvaccinated, the two vaccinated, and the two tuberculin-positive groups, permit both an assessment of the value of vole bacillus vaccination and a valid comparison of it with B.C.G. vaccination. The data are presented in this way in Section B of Tables II to IV. (Apart from those given vole bacillus vaccine, all the participants in Section B also appear in Section A.)

The children who entered when vole bacillus vaccine only was being given appear in neither of these comparisons. Because of their small numbers they add very little to the assessment of vole bacillus vaccination and are not considered further in the present report.

Contact with the Participants After They Left School

At the time when the representative samples of the records were drawn some participants had not been in the trial for more than eighteen months. The sample information on the effectiveness of the follow-up of the participants after they had left school is therefore complete for only eighteen months after entry, although there is some incomplete information for a further six months; the position is shown in Table II.

Section C of Table II summarizes the follow-up of the participants included in Sections A and B of the tables—that is, all those in Section A plus the vole-bacillus-vaccinated group in Section B. In all, 77% of the entrants had returned at least one postal inquiry form, 76% had been visited at home at least once, and 52% had had a chest radiograph taken after leaving school. During the period only 6% of the entrants were not in contact with the teams by any of these means.

The figures for the radiographic examinations do not give a true indication of the actual response of the participants to the invitations to attend. They were not invited to a follow-up examination until between ten and eighteen

months after leaving school ; however, most had entered the trial three to five months *before* leaving school. As a result, approximately one-third had no opportunity to attend for a radiograph after leaving and within eighteen months of entering the trial. Indeed, the incomplete information from the sample analysis beyond eighteen months (Table II) shows that at least a further 22% of the participants had a chest radiograph taken in the following six months, and this includes many of the 6% not previously brought in contact with the teams by the postal inquiry or the health visitor.

It is important to note from Sections A and B of Table II that the success of the follow-up was similar in all the skin-test and vaccination groups in each section. Thus any differences which may be observed in the incidence of tuberculosis between the groups are unlikely to be due to differences in the intensity of case-finding procedures.

Deaths in the First Two and a Half Years

The total number of participants known to have died within two and a half years of entering the trial was 38. None of the deaths was due to any form of tuberculosis. The principal causes of death were accidents (13), malignant disease (7), and pneumonia (3). There appear to be no more than chance differences between the mortalities in the five skin-test and vaccination groups.

III. THE IMMEDIATE EFFECTS OF VACCINATION

Complications of Vaccination

Leaflets describing the normal course of the vaccination reaction were given to the vaccinated children, and they were instructed to report any abnormality to the school medical officer. By these measures a few cases of regional adenitis with cold abscess formation, following both B.C.G. and vole bacillus vaccination, were brought to the notice of the teams, but there was no evidence that such complications were common. At the second examination at school very few complications, either of B.C.G. or of vole bacillus vaccination, were observed. Those that were found consisted of delayed healing of the vaccination lesion, with shallow ulceration ; the regional glands were not routinely examined. Certain other complications of vaccination were not discovered until later, and these are described below.

Conversion to Tuberculin Positivity Following Vaccination

A positive reaction to tuberculin following either B.C.G. or vole bacillus vaccination is generally regarded as a sign of satisfactory vaccination. Table III gives the results of the tests at the second examination at school, based on the representative samples of the participants. The findings in the negative unvaccinated group illustrate the effects of natural infection with tubercle bacilli in the period of three to five months between the two examinations at school, coupled with variations inherent in the performance of the tuberculin test. At the second examination, only 0.4% of these children were positive to 3 T.U. and a further 5.3% were positive to 100 T.U. only (Section A). In contrast, 85.8% of the B.C.G.-vaccinated group were positive to 3 T.U. and a further 13.8% to 100 T.U. only, representing a total of 99.6%. From Section B of Table III it will be seen that 59.8% of the children in the vole-bacillus-vaccinated group were positive to 3 T.U. and a further 34.6% to 100 T.U. only, giving a total of 94.4% converted. Compared with the figures for the children concurrently given B.C.G vaccine, the total percentage converted with vole bacillus vaccine was slightly smaller, and the percentage positive to 3 T.U. was considerably smaller.

The percentage converted was studied for each batch of vaccine as the trial proceeded, as a check both of the vaccination techniques and of the potency of the vaccines. It

TABLE II.—*Percentages of Participants Who Returned a Postal Inquiry Form, Who were Visited by a Health Visitor or Who had a Chest Radiograph taken after Leaving School (Estimates Based on Representative Samples)*

Section		Skin-test and Vaccination Group	No. of Participants	Within 18 Months of Entry to the Trial				Between 18 Months and 2 Years after Entry to the Trial
				Percentage Returned a Postal Inquiry Form	Percentage Visited by a Health Visitor	Percentage who had a Chest Radiograph Taken	Percentage Brought in Contact with the Teams by at Least One of These Means	Minimum Additional Percentage who had a Chest Radiograph Taken
A	Children admitted concurrently with those given B.C.G. vaccine	Negative unvaccinated	13,200	*83*	*77*	*51*	*96*	*26*
		Negative, B.C.G. vaccinated	14,100	*79*	*80*	*50*	*94*	*24*
		Positive to 3 T.U.	15,800	*75*	*73*	*57*	*94*	*17*
		Positive only to 100 T.U.	6,500	*77*	*77*	*50*	*95*	*25*
B	Children admitted concurrently with those given vole bacillus vaccine	Negative unvaccinated	6,400	*78*	*72*	*51*	*95*	*21*
		Negative, B.C.G. vaccinated	6,400	*73*	*76*	*48*	*92*	*21*
		Negative, vole bacillus vaccinated	6,400	*71*	*69*	*53*	*92*	*17*
		Positive to 3 T.U.	8,600	*70*	*69*	*59*	*94*	*16*
		Positive only to 100 T.U.	3,500	*70*	*73*	*44*	*93*	*25*
C	All participants included in the above comparisons*		56,000	*77*	*76*	*52*	*94*	*22*

* That is, all participants in Section A plus the vole-bacillus-vaccinated group in Section B.

TABLE III.—*Percentages of Participants, in the Negative Unvaccinated and in the Two Vaccinated Groups, who had Positive Tuberculin Reactions at the Second Examination at School (Estimates Based on Representative Samples of Participants).*

Section		Skin-test and Vaccination Group (On Entry to the Trial)	At the Second Examination at School			
			No. who Completed the Skin Test	Percentages with Positive Tuberculin Reactions		
				Positive to 3 T.U.	Positive Only to 100 T.U.	Total Positive
A	Children admitted concurrently with those given B.C.G. vaccine	Negative unvaccinated	5,700	*0·4*	*5·3*	*5·7*
		Negative, B.C.G. vaccinated	7,300	*85·8*	*13·8*	*99·6*
B	Children admitted concurrently with those given vole bacillus vaccine	Negative unvaccinated	2,600	*0·0*	*5·2*	*5·2*
		Negative, B.C.G. vaccinated	3,400	*84·5*	*14·5*	*99·0*
		Negative, vole bacillus vaccinated	3,600	*59·8*	*34·6*	*94·4*
C	*Period of vaccination*					
	Jan., 1951–July, 1951	Vole bacillus vaccinated	1,700	*29·4*	*58·8*	*88·2*
	Sept., 1951–Dec., 1952	Vole bacillus vaccinated	1,900	*87·5*	*12·5*	*100·0*

was found that the earlier batches of vole bacillus vaccine, given to approximately 2,300 participants (one-third of the total receiving this vaccine), produced low conversion, particularly to 3 T.U., compared with B.C.G. vaccine. On examination it was discovered that these batches were weaker than the standard originally intended. In September, 1951, the vaccine was brought up to standard, and thereafter, as illustrated in Section C of Table III, the percentages converted were almost identical with those for B.C.G. vaccine. The possible consequences of this variation in the strength of the vole bacillus vaccine will be studied in a later report.

Size of B.C.G. Vaccination Reactions

The average diameters of the B.C.G. vaccination reactions measured at the second examination at school (estimated from the samples) were 8.1 mm. for boys, vaccinated on the arm, and 9.9 mm. for girls, vaccinated on the thigh.

IV. THE CASES OF TUBERCULOSIS

Assessment of the Cases of Tuberculosis

All the definite and suspected cases of tuberculosis were reviewed by an independent assessor. To avoid bias this assessor was kept unaware of the results of any tuberculin tests and of whether any vaccination had been performed. A few cases of suspected tuberculosis of bones or joints, without bacteriological or histological confirmation, were referred to a second assessor, under the same conditions.

The assessor first decided from the series of radiographs and the findings of the clinical and other examinations whether the case was one of active tuberculosis. For some cases he decided that the disease was not tuberculosis; for a few others the evidence in favour of or against tuberculosis was inadequate, and these were classed as "possible" cases. For the cases of definite tuberculosis the assessor described the form of the disease, and the character, course, and maximal extent of any lesions apparent on the series of radiographs.

It was also important for the assessor to distinguish between cases of tuberculosis present at the time of entry to the trial and those arising after entry. Many of the cases which were present on entry had been detected at that time and the children excluded from the trial, but some children who were accepted into the trial were discovered only during the follow-up to have had tuberculosis on entry.

Finally, the assessor noted the date by which the disease first became manifest—that is, for pulmonary lesions, when the first abnormal radiograph was taken, and, for other lesions, when the first definite symptoms or signs were observed (irrespective of when the diagnosis of tuberculosis had been made). This date has been regarded as the starting-point of the illness. It will be appreciated that for some cases the starting-point may be a considerable time after the true, but unknown, date of onset of the disease.

Cases of Tuberculosis Present on Entry to the Trial

As stated above, children found by the teams to be suffering from definite or suspected tuberculosis at the first examination at school were excluded from participation in the trial, and those not already under the care of a clinic were referred for investigation. A recent review of these previously unsuspected cases has shown that 70 were considered by the chest clinic physicians to be of definite tuberculosis.

In addition, a total of 85 cases, discovered after the 56,700 participants had completed the first examination and had entered the trial, were judged by the independent assessor to have started before entry. Of these, 64 were previously unsuspected cases of definite tuberculosis, 7 were definite cases under the care of a clinic (unknown to the teams at the time of the first examination), and 14 were cases of possible tuberculosis. These 85 children should have been excluded from the trial and have therefore been excluded from all the tables which follow.

In 67 of the 85 cases the radiograph taken on entry showed, on re-scrutiny, abnormal appearances indicative of tuberculosis; in 1 case with a normal 35-mm. radiograph on entry there had been a pleural effusion two months earlier, and in 13 cases of non-pulmonary disease symptoms had been present before the participant entered the trial. There remain 4 cases of definite tuberculosis where the assessor decided that the disease must have been present at the time of entry, although the symptoms or lesions were not apparent until later. In one of them, symptoms of non-pulmonary disease appeared only three months after the child had entered the trial. In the other 3, pulmonary lesions were first seen on radiographs taken at the second examination at school; the 35-mm. radiograph on entry in one case was considered not to be of sufficiently high quality to exclude the presence of the lesion, and in another the film had been lost; in the third case the assessor considered that the lesion was probably present on entry but was obscured by bony shadow. These 4 children had (unknown to the assessor) all given a positive reaction to tuberculin on entry to the trial.

Tuberculous Lesions Attributed to Vaccination

In 5 participants, lesions which developed subsequent to B.C.G. or vole bacillus vaccination were brought to the attention of the teams as cases of tuberculosis and submitted to the assessor, but were regarded by him as complications of vaccination, to be classed with the complications referred to above. These were 2 cases of erythema nodosum, 1 case of tuberculous cervical adenitis, and 2 cases of tuberculous axillary adenitis, occurring one, one, three, six, and eight months respectively after entry to the trial. In the course of his assessment, the assessor suggested that if the participant had been vaccinated the lesions could have been due to the vaccinating organism. For these cases, and for no others, the assessor was then informed that the participant had been vaccinated. As a result, he attributed all 5 cases to the vaccinating organism. The 2 cases of erythema nodosum occurred in B.C.G.-vaccinated participants, and the 3 cases of tuberculous adenitis in vole-bacillus-vaccinated participants.

In addition, examinations of the vole-bacillus-vaccination sites during the follow-up revealed occasional lesions indistinguishable from lupus vulgaris, at or around the site of vaccination. These ranged from a few discrete pin-point lesions, corresponding to the original puncture marks, to a confluent lesion occupying the entire vaccination area or extending beyond it. Up to the end of June, 1955, a total of 22 cases severe enough to require treatment had been observed. These cases all occurred among the 4,100 participants given the vaccine after it had been brought up to standard (see above); 10 of the lesions were on the arm (among 2,100 boys), and 12 on the thigh (among 2,000 girls). Further information on all these lesions will be given in a later report. The B.C.G. vaccination sites were also examined, but no similar lesions were found.

All these lesions have been regarded as complications of vaccination, and none of the cases has been included in the tables which follow. It should be emphasized that there was no evidence that any of the other cases of tuberculosis in vaccinated participants were due to the vaccinating organism (see below).

Incidence of Tuberculosis in the First Two and a Half Years

By the end of June, 1955, every participant had been in the trial for at least two and a half years. The great majority of the cases of tuberculosis starting within two and a half years of entry may be presumed to have come by now (January, 1956) to the notice of the teams, and it is thus possible in the present report to compare the incidence of tuberculosis in the various skin-test and vaccination groups during this thirty-month follow-up.

A total of 165 cases of definite tuberculosis started within thirty months of entry to the trial, and a further 9 were assessed as possible tuberculosis. Of the definite cases 75 were first discovered by the teams through their radiographic examinations, and 90 came to the notice of the teams after discovery by the National Health Service. As stated above, there were no deaths from tuberculosis during this period.

The numbers of cases in the various skin-test and vaccination groups are given in Table IV. Section A, which contains the findings for all the children given B.C.G. vaccine, and for those admitted concurrently in the other skin-test and vaccination groups, shows that there were 64 cases compared with 17 cases among the 8,700 entrants giving reactions of 5 to 14 mm. induration to 3 T.U., or an annual incidence of 0.78 per 1,000. The difference is statistically significant (0.001> P). The subsequent incidence of tuberculosis among those with the smaller reactions to 3 T.U. was almost the same as that in the group positive only to 100 T.U. In this latter group the number of cases is small, and no association was apparent between size of reaction to tuberculin and subsequent incidence of tuberculosis.

Table IV also shows that there were only 9 cases where the assessor was in doubt over the diagnosis. The above comparisons would have remained practically unaltered if these possible cases had been included with the definite cases.

TABLE IV.—*Cases of Tuberculosis Starting Within Two and a Half Years of Entry to the Trial**

Section		Skin-test and Vaccination Group	Estimated No. of Participants	Definite Cases of Tuberculosis		Possible Cases of Tuberculosis Starting within 30 Months
				No. Starting within 30 Months	Annual Incidence per 1,000 Participants	
A	Children admitted concurrently with those given B.C.G. vaccine	Negative unvaccinated	13,200	64	1·94	2
		Negative, B.C.G. vaccinated	14,100	13	0·37	2
		Positive to 3 T.U.	15,800	69	1·75	3
		Positive only to 100 T.U.	6,500	12	0·74	1
B	Children admitted concurrently with those given vole bacillus vaccine	Negative unvaccinated	6,400	33	2·06	2
		Negative, B.C.G. vaccinated	6,400	5	0·31	1
		Negative, vole bacillus vaccinated	6,400	7	0·44	1
		Positive to 3 T.U.	8,600	37	1·72	2
		Positive only to 100 T.U.	3,500	6	0 69	0
C	All participants included in the above comparisons†		56,000	165	—	9

* For the definition of the starting-point of the illness, see text. † That is, all participants in Section A plus the vole-bacillus-vaccinated group in Section B.

in the tuberculin-negative unvaccinated group, giving an annual incidence of 1.94 cases per 1,000 participants. With 13 cases, the annual incidence in the B.C.G.-vaccinated group was much lower, being 0.37 per 1,000, approximately one-fifth of the rate in the negative unvaccinated group. The possibility of this difference having occurred by chance is very remote (less than 1 in a million). The annual incidence in the first thirty months after entry among those initially positive to 3 T.U. was rather less than that in the negative unvaccinated group—namely, 1.75 per 1,000; among those positive only to 100 T.U. the annual incidence was 0.74 per 1,000. This difference in incidence between the two positive groups is statistically significant (0.01>P>0.001), and so is that between the negative unvaccinated group and those positive only to 100 T.U. (0.01> P>0.001). The incidence in the B.C.G.-vaccinated group is also substantially and significantly lower than that in the group initially positive to 3 T.U. (0.001>P), but, while rather less, does not differ significantly from that in the group positive only to 100 T.U. (0.2>P>0.1).

Section B of Table IV contains the findings for children given vole bacillus vaccine and those for the children (already included in Section A) who were admitted concurrently in the other skin-test and vaccination groups. Compared with the negative unvaccinated group there was a low incidence of tuberculosis in the vole-bacillus-vaccinated group, the annual rates being respectively 2.06 and 0.44 per 1,000 participants; the possibility of this difference having occurred by chance is small (less than 1 in 10.000). The difference between the annual rates for the vole-bacillus-vaccinated group (0.44) and for the concurrent group of B.C.G.-vaccinated children (0.31) does not attain statistical significance.

Within the group initially positive to 3 T.U. there was an association (not shown in Table IV) between the diameter of induration recorded at the tuberculin test on entry and the subsequent incidence of tuberculosis. Among the 7,100 entrants giving reactions of 15 mm. induration or more to 3 T.U., 52 definite cases of tuberculosis started within thirty months, representing an annual incidence of 2.93 per 1,000.

Vaccination Reactions and Tuberculin Tests in Cases of Tuberculosis Occurring in Vaccinated Participants

The results of examinations subsequent to entry for the 20 definite cases of tuberculosis in the two vaccinated groups are summarized in Tables V and VI. Nine cases (B.C.G. 1, 3, 4, 5, 6, 7, 8, and Vole 1, 5) were observed to have a positive reaction to tuberculin in conjunction with a normal chest radiograph between two and six months after vaccination, and a healed vaccination reaction was also observed either then or later. One more case (B.C.G. 11) had no second examination at school, but similar observations were made thirteen months after vaccination. One case (Vole 6) had a positive reaction to tuberculin and a healed vaccination reaction three months after vaccination, but no radiograph was taken. In 2 cases (Vole 3 and 4) no vaccination reaction was seen on examination, but each was positive to tuberculin and had a normal chest radiograph four months after vaccination. Six cases (B.C.G. 2, 9, 10, 12, 13, and Vole 7) had no tuberculin test after entry and before the disease had developed, but in all 6 a healed vaccination reaction was observed at some time. Thus, in all 13 B.C.G.-vaccinated cases and in 6 of the 7 vole-bacillus-vaccinated cases, there is evidence that the participants had been satisfactorily vaccinated, as judged by the usual criteria, although for case B.C.G. 9, the only one known to have developed within six months of vaccination, the disease could well have arisen before any protection had been conferred.

For the remaining case (Vole 2) the vaccination site was not examined, nor was a tuberculin test given, until five months after the tuberculous pleural effusion. At this time (two years after entry to the trial), no vaccination reaction was seen, and so it is possible that this case had not been satisfactorily vaccinated. It has, however, been observed in the course of the trial that, with the multiple-puncture technique for vole bacillus vaccination, the vaccination reactions frequently become less obvious and may disappear (as, for example, in cases Vole 5 and 6). Cases Vole 1, 2, 3, and 4 were all admitted to the trial during the period when the vole bacillus vaccine was producing a low percentage conversion (see above).

TABLE V.—*Summary of Results of Examinations of B.C.G.-vaccinated Participants who Developed Definite Tuberculosis within Two and a Half Years of Entry to the Trial*

B.C.G. Case No.	Date of Vaccination	Results of Examinations Subsequent to Vaccination				Interval Between Vaccination and Starting-point of Illness, in Months*
		Interval Between Vaccination and Examination, in Months*	Chest Radiograph	Vaccination Reaction	Tuberculin Test	
1	18/1/51	3	Normal	9 mm.	+3 T.U.	29
		15	Normal	..	+3 T.U.	
		29	Pulmonary tuberculosis	..	+3 T.U.	
2	22/2/51	31	Pleural thickening from previous effusion	5 mm.	+3 T.U.	30 (Pleurisy)
3	1/3/51	4	Normal	Present but not measured	+3 T.U.	15
		15	Pulmonary tuberculosis	..	..	
4	5/3/51	3½	Normal	..	+3 T.U.	27
		15	Normal	..	..	
		27	Pulmonary tuberculosis	5 mm.	+3 T.U.	
5	21/6/51	4½	Normal	8 mm.	+3 T.U.	29
		29	Pleural effusion	..	..	
6	28/6/51	2	Normal	8 mm.	+3 T.U.	27
		20	Normal	..	..	
		27	Pulmonary tuberculosis	..	..	
7	28/6/51	2	Normal	9 mm.	+3 T.U.	16 (Erythema nodosum)
		16	Hilar gland enlargement	..	+10 T.U. (at hospital)	
8	9/7/51	3	Normal	9 mm.	+3 T.U.	28
		12	Normal	..	..	
		28	Pulmonary tuberculosis	9 mm.	+3 T.U.	
9	15/10/51	3	Pulmonary tuberculosis	7 mm.	+3 T.U.	3
10	18/2/52	13	Normal	6 mm.	..	28
		28	Pulmonary tuberculosis	..	+3 T.U.	
11	10/3/52	13	Normal	..	+3 T.U.	29
		29	Pulmonary tuberculosis	8 mm.	+3 T.U.	
12	15/9/52	13	Pulmonary tuberculosis	..	+3 T.U.	13
		23	Pulmonary tuberculosis	10 mm.	..	
13	11/12/52	14	Pulmonary tuberculosis	7 mm.	+3 T.U.	14

* To the nearest half month up to six months, and to the nearest month thereafter.

TABLE VI.—*Summary of Results of Examinations of Vole-Bacillus-Vaccinated Participants who Developed Definite Tuberculosis within Two and a Half Years of Entry to the Trial*

Vole Case No.	Date of Vaccination	Results of Examinations Subsequent to Vaccination				Interval Between Vaccination and Starting-point of Illness, in Months*
		Interval Between Vaccination and Examination, in Months*	Chest Radiograph	Vaccination Reaction	Tuberculin Test	
1	16/2/51	2½	Normal	Weak	+100 T.U.	22
		16	Normal	..	..	
		22	Pulmonary tuberculosis	..	..	
2	8/3/51	20	Pleural effusion	..	..	19 (Pleurisy)
		24	Pleural thickening from previous effusion	None	+10 T.U. (at hospital)	
3	31/5/51	4	Normal	None	+100 T.U.	15 (Pleurisy)
		17	Pleural effusion	..	..	
4	9/7/51	4½	Normal	None	+3 T.U.	26
		26	Pulmonary tuberculosis	..	..	
5	18/10/51	5½	Normal	Weak	+100 T.U.	21
		20	Normal	None	+3 T.U.	
		21	Pulmonary tuberculosis	..	+10 T.U. (at chest clinic)	
6	11/2/52	3½	..	Strong	+3 T.U.	29 (Pleurisy)
		31	Pleural effusion	None	+3 T.U.	
7	20/10/52	15	Normal	Strong	..	20 (Symptomatic onset of non-pulmonary tuberculosis)
		21	Normal	..	+10 T.U. (at hospital)	

* To the nearest half month up to six months, and to the nearest month thereafter.

The Forms of Tuberculosis

The forms of tuberculosis which occurred in the various skin-test and vaccination groups are shown in Table VII. If two or more were present the case was assigned to the major form; for example, tuberculous meningitis took precedence over any other form, and pulmonary tuberculosis took precedence over a pleural effusion. A division of the cases of pulmonary tuberculosis into those showing primary and other pulmonary lesions was considered, but, in view of the difficulties inherent in classifying tuberculosis radiographically in adolescents on these lines, no such grouping is used in the present report. The occurrence of hilar gland enlargement, indicative of a primary lesion, is studied below.

Pulmonary tuberculosis was observed in 104 of the 165 cases (63%), and occurred in all the skin-test and vaccination groups. Although the numbers of cases in the two vaccinated groups are small, there is no evidence of important differences between the five groups in the ratio of the number of pulmonary to the total cases.

Tuberculous pleural effusion, without evidence of pulmonary tuberculosis, was the next most numerous form, with 36 cases (22%). In addition, a pleural effusion preceded, or was discovered at the same time as, the pulmonary lesions in 8 more cases. The ratio of the number of pleural effusions to the total cases was greater among those initially positive only to 100 T.U. (5 of 12) than among those positive to 3 T.U. (12 of 69), but the difference is not statistically significant. The negative unvaccinated group (22 of 64) and the vaccinated groups combined (5 of 20) occupied an intermediate position in this respect.

Hilar gland enlargement, with no other lesion, was noted in only 1 case, which was in the negative unvaccinated group. It was also found, however, in association with other lesions (mainly pulmonary lesions, pleural effusions, or both) in 17 more cases. In all, hilar gland enlargement was observed in a larger proportion of the cases in the negative unvaccinated group than in the vaccinated groups (14 of 64 compared with 1 of 20), although on these numbers the difference is not statistically significant; hilar gland enlargement was noted in 1 of the 69 cases in those initially positive to 3 T.U. and in 2 of the 12 in those initially positive only to 100 T.U.

There were 3 cases of tuberculous meningitis, all in the negative unvaccinated group, 1 of which was associated with miliary pulmonary tuberculosis, and 1 both with miliary pulmonary tuberculosis and with a pleural effusion. In addition, 3 of the pulmonary lesions, also in the negative unvaccinated group, were of miliary type. Thus tuberculous meningitis, miliary pulmonary tuberculosis, or both, occurred in 6 of the 64 cases in the negative unvaccinated group. None occurred in any of the other groups.

Nature and Maximal Extent of the Pulmonary Lesions

The pulmonary lesions were classified by the independent assessor according to their maximal radiographic extent up to the time when the assessment was made, as shown in Table VIII. Of the 104 pulmonary cases in all groups, 3, just referred to, showed lesions of miliary type. Of the cases with other pulmonary lesions, 35 showed cavitation on radiographic examination; in 25 of these the entire lesion involved more than two rib interspaces. The remaining 66 cases had pulmonary lesions without cavitation; in 7 the total extent of the lesions involved more than two rib interspaces, in 43 their extent was greater than 6 sq. cm. but did not involve more than two interspaces, and in only 16 was their extent 6 sq. cm. or less (on a full-size chest radiograph).

Cases with cavitation were observed in all the groups, being found in 13 of the 39 cases in the negative unvaccinated group, in 6 of the 13 cases in the vaccinated groups combined, and in 16 of the 52 cases in the tuberculin-positive groups combined. Although the total number of pulmonary cases in some of the groups is small, the distribution offers no evidence of important differences in the nature or extent of the pulmonary lesions between the groups. The protection afforded by the vaccines thus does not appear to be limited to the prevention of lesions of a particular nature or extent.

Action taken by the Physician in Charge of the Patient

Further evidence of the serious nature of many of the cases of tuberculosis which occurred is provided by Table IX. Of the 165 patients, 113 (68%) were taken off work for a period of at least three months. Of these 113 patients,

TABLE VII.—*Definite Cases of Tuberculosis Starting Within Two and a Half Years of Entry to the Trial, According to the Form of the Disease*

Skin-test and Vaccination Group	Total Cases	Form of Tuberculosis						
		Pulmonary Tuberculosis	Tuberculous Pleural Effusion*	Hilar Gland Enlargement†	Tuberculous Meningitis	Bone or Joint Tuberculosis	Tuberculous Cervical Adenitis	Other Forms
Negative unvaccinated	64	39	17	1	3	0	3	1‡
Negative, B.C.G. vaccinated	13	10	2	0	0	0	0	1§
Negative, vole bacillus vaccinated	7	3	3	0	0	1	0	0
Positive to 3 T.U.	69	45	10	0	0	3	8	3‖
Positive only to 100 T.U.	12	7	4	0	0	0	0	1¶
All groups	165	104	36	1	3	4	11	6

* Without evidence of pulmonary tuberculosis. † Without other evidence of tuberculosis. ‡ Tuberculous peritonitis with small associated pulmonary lesion. § Erythema nodosum with associated hilar gland enlargement. ‖ 1 tuberculous peritonitis; 1 tuberculous epididymitis; 1 lupus vulgaris. ¶ Tuberculous axillary adenitis.

TABLE VIII.—*Definite Cases of Pulmonary Tuberculosis Starting Within Two and a Half Years of Entry to the Trial, According to the Nature and Maximal Extent of the Pulmonary Lesions*

Skin-test and Vaccination Group	Total Pulmonary Cases	Miliary Type of Lesions	Lesions with Cavitation		Lesions without Cavitation		
			Lesions Involving More than 2 Rib Interspaces	Lesions Involving Up to 2 Rib Interspaces	Involving More than 2 Rib Interspaces	More than 6 sq. cm. in Extent, Involving Up to 2 Rib Interspaces	Up to 6 sq. cm. in Extent
Negative unvaccinated	39	3	9	4	3	15	5
Negative, B.C.G. vaccinated	10	0	4	1	1	1	3
Negative, vole bacillus vaccinated	3	0	1	0	0	2	0
Positive to 3 T.U.	45	0	10	3	3	22	7
Positive only to 100 T.U.	7	0	1	2	0	3	1
All groups	104	3	25	10	7	43	16

TABLE IX.—*Definite Cases of Tuberculosis Starting Within Two and a Half Years of Entry to the Trial, According to the Action Taken by the Clinician*

Skin-test and Vaccination Group	Total Cases	Taken Off Work and Treated		Remaining at Work under Observation
		For 3 Months or More	For Less than 3 Months	
Negative unvaccinated	64	45	4	15
Negative, B.C.G. vaccinated	13	8	0	5
Negative, vole bacillus vaccinated	7	6	0	1
Positive to 3 T.U.	69	44	7	18
Positive only to 100 T.U.	12	10	2	0
All groups	165	113	13	39

88 received chemotherapy, collapse therapy, or surgery, in addition to rest in bed; 16 of the remaining 25 were cases of pleural effusion. At the other extreme, 39 patients (24%) remained at work and were kept under observation; 1 of these patients also received some chemotherapy.

Of the 64 patients in the negative unvaccinated group, 45 were taken off work for three months or more; similarly, 14 of the 20 patients in the vaccinated groups combined, 44 of the 69 in the group positive to 3 T.U., and 10 of the 12 in the group positive only to 100 T.U. were taken off work for three months or more. Bearing in mind the small numbers of cases in some groups, there is again no evidence of important differences between the groups in regard to the severity of the lesions, as judged by the action taken by the physician responsible for the care of the patient.

Bacteriological and Pathological Investigations

Of the 104 cases of pulmonary tuberculosis, 8 had no bacteriological examinations at any time. Positive bacteriological results were obtained in 41 of the remaining 96 cases. In 5 of the 55 cases with negative bacteriological results the examinations were made only after the start of chemotherapy, but the other 50 all had negative results at a time when no chemotherapy had been given. Since the investigation and treatment of all cases were carried out at local chest clinics and were not the responsibility of the unit physicians, there was no opportunity for the unit to carry out intensive bacteriological examinations, and in many instances no special emphasis was laid upon these tests in the routine management of the cases. The proportion of cases confirmed bacteriologically is therefore relatively low.

In all, tubercle bacilli were isolated from 16 of the 39 cases of pulmonary tuberculosis in the tuberculin-negative unvaccinated group, from 5 of the 10 cases in the B.C.G.-vaccinated group, from 2 of the 3 in the vole-bacillus-vaccinated group, from 14 of the 45 in those positive to 3 T.U., and from 4 of the 7 in those positive only to 100 T.U. The organisms isolated from the 5 cases in the B.C.G.-vaccinated group and from the 2 in the vole-bacillus-vaccinated group were found to be virulent and of human type.

A specimen of the fluid was examined in only 18 of the 36 cases of pleural effusion classified as tuberculous: in 15 the fluid was sterile, and in 10 of these a high proportion of lymphocytes was recorded; in the other 3 cases (none vaccinated) tubercle bacilli were cultured from the fluid. In all 4 cases of tuberculosis of bones or joints, and in 7 of the 11 cases of cervical adenitis, the diagnosis was established by histological examination; in 1 of the remaining 4 cases of cervical adenitis the diagnosis was confirmed bacteriologically. The 3 cases of tuberculous meningitis were all confirmed by bacteriological examination of the cerebrospinal fluid.

Reliability of the Independent Assessments

It is conceivable that the withholding of information on the results of skin tests, essential though it is for an unbiased comparison between the various groups, might have resulted in some cases being incorrectly diagnosed by the assessor. It is therefore of interest to compare his diagnosis with that of the chest clinic or other physician taking charge of the case. For 157 of the 165 definite cases of tuberculosis arising after entry and accepted for this report there was agreement on diagnosis between assessor and physician in charge; 5 of the 8 disagreements concerned pleural effusions regarded by the assessor as due to tuberculosis, but by the physician in charge as due to non-tuberculous conditions. Of the other 3 cases, 2 were regarded as possible pulmonary tuberculosis, and 1 as not pulmonary tuberculosis, by the physician in charge. Four of these 8 disagreements were in the negative unvaccinated group and 4 in the group positive to 3 T.U. In addition to the 165, 7 cases were regarded by the physician in charge, but not by the assessor, as tuberculous; 3 of these were considered by the assessor to be possible cases; in the other 4 he decided that there was no evidence of tuberculosis. Three of these 7 cases were in the negative unvaccinated group, 2 were in the B.C.G.-vaccinated group, and 2 were in the group positive to 3 T.U.

Further confirmation of the reliability of the independent assessments is provided by the results of tuberculin tests subsequent to entry, for the cases in the originally tuberculin-negative unvaccinated group classed as definite tuberculosis by the assessor. Of the 64 cases, 57 became tuberculin positive between entry to the trial and the development of the disease; 6 cases had no tuberculin tests during this period, but the diagnosis of tuberculosis was confirmed in 5 bacteriologically and in 1 histologically; the remaining case (one of the disagreements of diagnosis referred to above) had a negative reaction to 10 T.U. in hospital at the time of the pleural effusion.

Supplementary evidence on the same point is provided by the results of the initial tuberculin tests for the cases classed by the assessor as definite tuberculosis present on entry. Of the 71 cases, 64 were positive to 3 T.U. and 4 were positive only to 100 T.U. The remaining 3 were in the negative unvaccinated group. In 2, pleurisy followed by pulmonary tuberculosis was discovered after entry to the trial, but the assessor classed them as having had tuberculosis on entry because he noted hilar gland enlargement on one of the initial 35-mm. radiographs, and pleural thickening on the other; in both cases sensitivity to tuberculin developed after entry. The third case was regarded as tuberculous cervical adenitis both by the assessor and by the surgeon who treated the case two months before entry to the trial.

Starting-point of the Illness

As already described, the assessor decided retrospectively, from the detailed records of each case of tuberculosis, the date of the earliest radiographic or clinical manifestation of the disease, which has been regarded as the starting-point of the illness. The intervals between entry to the trial and the starting-point of the illness are given in Table X. Of the 165 definite cases, 21 had a starting-point within six months of entry, 13 between six months and one year, 42 between one year and eighteen months, 41 between eighteen months and two years, and 48 between two years and thirty months. These figures incidentally demonstrate the defects of the starting-point (as here defined) as a measure of the time of onset of the disease; the number of cases with starting-points between six months and one year is less than that before and after, probably because relatively few participants had a radiographic examination by the teams during this period, and not because of a low incidence of the disease. However, this disadvantage applies equally in all the skin-test and vaccination groups, and so does not invalidate comparisons between them.

Only 1 case in a vaccinated participant had a starting-point within six months of entry, whereas, from the experience in the negative unvaccinated group, 6.3 cases would have been expected in the two vaccinated groups combined. This indicates that the vaccines confer protection soon after being given. Between six and twenty-four months the actual and

TABLE X.—*Definite Cases of Tuberculosis, According to the Interval Between Entry and the Earliest Radiographic or Clinical Manifestation (the Starting-point) of the Illness*

Skin-test and Vaccination Group	Total Cases Starting within 30 Months of Entry	Months between Entry to the Trial and the Starting-point of the Illness							Cases Starting between 30 Months and 4 Years after Entry
		0–	6–	12–	18–	24–	30– (Incomplete)	36– (Incomplete)	42–48 (Incomplete)	
Negative unvaccinated	64	4	4	14	21	21	15	13	10	38
Negative, B.C.G. vaccinated	13	1	0	4	0	8	5	0	0	5
Negative, vole bacillus vaccinated	7	0	0	1	4	2	0	0	0	0
Positive to 3 T.U.	69	14	9	17	15	14	11	5	8	24
Positive only to 100 T.U.	12	2	0	6	1	3	3	3	2	8
All groups	165	21	13	42	41	48	34	21	20	75

expected numbers of cases in vaccinated participants in the successive six-month periods were 0 and 5.4, 5 and 22.8, and 4 and 33.3. There were 10 cases in vaccinated participants with starting-points between twenty-four and thirty months after entry, whereas from the experience in the negative unvaccinated group 33.3 cases would have been expected. Thus the vaccines still confer substantial protection between twenty-four and thirty months.

Table X shows a change during the first two years in the relative incidence of tuberculosis in the negative unvaccinated group and in the group positive to 3 T.U. In the first six months, only 4 cases started in the negative unvaccinated group, compared with 14 in those positive to 3 T.U.; between six months and one year the numbers were 4 and 9; between one year and eighteen months 14 and 17; and between eighteen months and two years 21 in the negative unvaccinated group but only 15 in those positive to 3 T.U. These trends indicate that the importance of the negative unvaccinated group as a source of cases of tuberculosis, relative to the group positive to 3 T.U., was increasing during the two years. However, it is not possible to determine whether the incidence of tuberculosis was really increasing in the negative unvaccinated group during the two years, and remaining uniform in the group positive to 3 T.U., because the starting-points depend to some extent upon the frequency of radiographic examinations, which varied from period to period; full information on these variations and their effects is not yet available.

Supplementary Information on Cases of Tuberculosis Starting After the First Two and a Half Years

There is some preliminary information on the continuance, beyond the first two and a half years, of the protection afforded by the vaccines. All the participants have now (January, 1956) been in the trial for three years, some have been in for as long as four years, and a small proportion, who entered at the beginning of the intake, have completed five years. All definite cases of tuberculosis with starting-points more than thirty months after entry are being assessed as they come to the notice of the teams, in exactly the same way as those with starting-points within thirty months, and the present totals up to four years are shown in Table X, according to the interval since entry. Although the numbers of cases become progressively less complete as the interval since entry increases, this does not invalidate comparisons between the various skin-test and vaccination groups.

Of the definite cases with starting-points between two and a half and four years after entry, 38 were in the negative unvaccinated group and only 5 in the B.C.G.-vaccinated group. A comparison with the corresponding totals of 64 and 13 for the first thirty months shows no evidence of any diminution in the efficacy of B.C.G. vaccine up to four years. In particular, the sudden rise in the number of cases starting in the B.C.G.-vaccinated group, from 0 between eighteen and twenty-four months, to 8 in the following six months, which, in the absence of later information, might have indicated a waning in the efficacy of B.C.G. vaccine, appears to be no more than an unusually large fluctuation in the emergence of cases in this group.

Of the 38 cases starting between two and a half and four years after entry in the negative unvaccinated group, 21 (not shown separately in Table X) occurred among participants admitted concurrently with those given vole bacillus vaccine, compared with none in the vole-bacillus-vaccinated group. The corresponding numbers of cases in the first thirty months were 33 and 7. Thus there is also no evidence of any diminution in the efficacy of vole bacillus vaccine up to four years.

V. DISCUSSION

Although it is now more than thirty years since B.C.G. vaccine was first used in man, the investigation described in this progress report is the first controlled trial of the vaccine to be undertaken in Great Britain, and one of the few so far undertaken in any part of the world. The early results of the present trial provide clear evidence, for a period of two and a half years, of the efficacy of B.C.G. vaccination, and also of vole bacillus vaccination, in the prevention of tuberculosis in the particular group of adolescents studied, and in the present circumstances in this country.

Features of the Trial

In addition to the inclusion of a comparative assessment of vole bacillus vaccine, the trial embodies a number of other important features. First, the effects of the two vaccines are being studied in adolescence under the ordinary conditions of urban and suburban life prevailing in an industrial community with well-developed health services and with relatively low tuberculosis incidence and mortality. The findings are therefore of special relevance to the control of tuberculosis in such a community.

Secondly, entry to the trial was confined to a narrow and susceptible age group—namely, to children who volunteered with parental consent in their final year at secondary modern schools in or near North London, Birmingham, and Manchester, when nearly all of them were aged between 14½ and 15 years. Moreover, those found, as a result of an examination which included a chest radiograph, to be suffering from any form of tuberculosis, and those found to be in contact at home with a case of pulmonary tuberculosis at the time of entry, were excluded from the trial. The 56,700 participants thus come from a wide range of social and economic backgrounds, they represent a clearly defined section of the population, and they were initially free both from active tuberculosis and from known contact with the disease at home.

A third feature in the design of the trial, which is of fundamental importance in the interpretation of the results, is that the children with negative reactions to tuberculin on entry were allocated by a random process to three groups; those in one group were left unvaccinated, those in another received B.C.G. vaccine, and those in the third group received vole bacillus vaccine. These three groups of participants can therefore be regarded as alike on entry to the trial, apart from their vaccination state, and they have been observed and examined subsequently to a similar extent. In addition, the children with positive reactions to tuberculin on entry have been followed in the same way as those with

negative reactions. A knowledge of the relative incidence of tuberculosis in all these groups is necessary for an assessment of the reduction to be expected in the total incidence of tuberculosis as a result of vaccination.

Fourthly, special efforts have been made to keep in close and frequent touch with all the participants through postal inquiries and home visits, and to use every available source of information to discover the cases of tuberculosis which have developed among them. A most important aspect of the follow-up has been that, in addition to access to chest clinic and other routine records of the National Health Service, there has been a scheme for the regular radiographic examination of the participants. As a result it is probable that few cases of tuberculosis have escaped detection ; it is an indication of the success of the various approaches that many cases have independently come to the notice of the investigating teams through more than one channel.

Fifthly, when the trial was planned, emphasis was laid upon the need to detect and study the cases of tuberculosis rather than the deaths ; in the event 165 of the participants are known to have contracted tuberculosis within two and a half years of entering the trial, but there was no death from the disease during this period.

It must be emphasized that, for a full evaluation of the two vaccines, a much longer period of observation than two and a half years will be necessary, but the early results of the trial are of sufficient importance to be considered in this progress report. The scope of the report is also limited because the numbers of participants (though not the numbers of cases of tuberculosis) had to be estimated from representative samples of the records, so that the first results should be available rapidly.

All cases in which tuberculosis was considered to be even a possible diagnosis were assessed by an independent assessor who, to avoid bias, was kept unaware of the results of any tuberculin tests and of whether the participant had or had not been vaccinated. There was a close correspondence between his diagnoses and those of the chest clinic or other physicians responsible for the investigation and treatment of the cases. The assessor decided that there was a total of 165 definite cases of tuberculosis in which the illness had begun after, but within thirty months of, entry to the trial.

Protection Afforded by Vaccination

As a consequence of the random allocation process, and because of the absence of bias, both in the intensity of the follow-up and in the assessment of the cases, any differences in the incidence of tuberculosis between the tuberculin-negative unvaccinated and the two vaccinated groups may be attributed directly to the vaccination. Although those who were vaccinated were told the expected course of the vaccination reaction, and therefore knew that they had been vaccinated, it is hard to see how this knowledge could have influenced the comparison. Indeed, despite the explanations given, many of those who received only tuberculin tests were under the impression that they too had been vaccinated.

In the first thirty months of observation, the number of definite cases of tuberculosis among 13,200 participants who were tuberculin negative on entry and were left unvaccinated was 64, giving an annual incidence of 1.94 per 1,000. In contrast, there were only 13 cases among the 14,100 participants, also tuberculin negative on entry, who received B.C.G. vaccine, giving an annual incidence of 0.37 per 1,000, or approximately one-fifth of the rate in the negative unvaccinated group. Between the ages of 15 and 17 years, and during the transition from school life to early employment, in an urban or suburban environment, B.C.G. vaccine therefore confers a substantial degree of protection against tuberculosis.

The number of cases of tuberculosis among 6,400 vole-bacillus-vaccinated participants during the thirty months following vaccination was 7, representing an annual incidence of 0.44 per 1,000, or approximately one-fifth of the incidence of 2.06 per 1,000 among those admitted concurrently to the tuberculin-negative unvaccinated group. The benefit to those given vole bacillus vaccine is thus substantial. Its efficacy appears to be very similar to that of B.C.G. vaccine ; the difference in incidence between the two vaccinated groups could well have arisen by chance. Moreover, the earlier batches of vole bacillus vaccine, which gave unexpectedly low percentages of subsequent positive reactions to tuberculin, were found to have been weaker than the standard originally intended ; the strength of the subsequent batches of vaccine was adjusted to this standard. Four cases of tuberculosis occurred among 2,300 participants given vole bacillus vaccine during the earlier period, and 3 among 4,100 given the vaccine in the later period.

There have been a few other trials of B.C.G. vaccine, in general population groups, in which the subjects found to be tuberculin negative were selected by a random process either for vaccination or to be left unvaccinated. In most of these trials the populations had low standards of living and high tuberculosis rates. Outstanding is the trial in North American Indians, which started in 1936 (Aronson, 1948 ; Aronson and Aronson, 1952 ; Stein and Aronson, 1953). About 1,500 tuberculin-negative subjects from infancy up to the age of 20 years were given B.C.G. vaccine, and a similar number were left unvaccinated ; those initially tuberculin positive were not followed up. The morbidity from tuberculosis, as judged by annual radiography and tuberculin tests, was studied for eleven years, and the mortality has been reported for fifteen years. A substantial degree of protection was demonstrated which was sustained for ten years ; there was a suggestion that it might wane thereafter. In 1949–50 the U.S. Public Health Service began studies on American Indian and on Puerto Rican schoolchildren, but Palmer and Shaw reported in 1953 that there were still too few cases to provide any definite evidence of the effectiveness of B.C.G. vaccine, though some protection was suggested. Sergent, Cantanei, and Ducros-Rougebief (1954) reported a clear effect of B.C.G. vaccine, given orally at birth, and again at one and three years, upon the mortality from all causes up to the age of 5 years, among Muslim children in Algiers.

The investigation of B.C.G. vaccine in a population group most closely approximating to that of the present trial is that in progress under the U.S. Public Health Service among all the 10,000 who were schoolchildren in Muscogee County, Georgia, in 1947. There were 4,800 negative reactors to tuberculin, 2,500 of whom, chosen at random, were given B.C.G. vaccine. No cases of tuberculosis have been reported in six years among either the vaccinated or the tuberculin-negative unvaccinated children, and only 5 among the 5,200 who were initially tuberculin positive (Palmer and Shaw, 1953). This investigation covers a wider and generally less vulnerable age group than that of the present trial, and for case-finding relies solely upon the established system of notification of cases of tuberculosis.

In a retrospective investigation of Swedish conscripts, who were offered B.C.G. vaccination on entry to the army, Dahlström and Difs (1951) and Dahlström (1953) found that the vaccine did not appear to confer protection against primary tuberculosis until two months had elapsed since vaccination, nor against other forms of tuberculosis until six months had elapsed. In the present trial, both vaccines appeared to confer protection within six months, and protection was still substantial between two and two and a half years after vaccination. Supplementary incomplete information suggests that the protection is maintained up to four years. As already stated, Aronson and Aronson (1952) reported that in North American Indians the substantial degree of protection was sustained for at least ten years.

When the forms of tuberculosis and their severity (as judged by several criteria) were studied for the 64 cases in the negative unvaccinated group, it was clear that most would be regarded as clinically important. A comparison with the corresponding information for the 20 cases in the two vaccinated groups combined suggests that the disease took

similar forms, and that the lesions were as extensive and severe, in the vaccinated participants. However, there were 3 cases of tuberculous meningitis and 3 of miliary pulmonary tuberculosis in the negative unvaccinated group, and none in either of the vaccinated groups. Again, hilar gland enlargement, indicative of primary tuberculosis, was noted in 14 of the 64 cases in the negative unvaccinated group, and in only 1 of the 20 cases among those vaccinated. In view of the difficulty found in distinguishing radiographically between primary and other pulmonary lesions in adolescents, no such classification has been used in the present report.

Complications of Vaccination

Complications attributable to vaccination have to be set against the efficacy of the vaccines in preventing tuberculosis. With each vaccine, regional adenitis and delayed healing of the vaccination lesion were occasionally recorded. In addition, among the 14,100 participants given B.C.G. vaccine, 2 cases of erythema nodosum developed after four weeks, and were attributed to the vaccine. The findings of Wylie, Bennett, and Swithinbank (1954) and Frew, Davidson, and Reid (1955) have also been confirmed, that lesions at the site of vaccination, indistinguishable from lupus vulgaris, develop in a number of those given vole bacillus vaccine. In 22 of 4,100 participants given the standard strength of vaccine in the present trial, these lesions have been sufficiently severe to require treatment; no lesions requiring treatment were found among 2,300 participants given the substandard vaccine, but the conversion rates to tuberculin positivity were not so high for this group as for those given the standard vaccine. It should be noted, further, that the vole bacillus vaccine was administered by multiple puncture, and it is possible that the intracutaneous method, which is in use in Czechoslovakia (Šula, 1955) and is being explored in this country (Wells and Wylie, 1955), will not produce this complication.

Incidence of Tuberculosis in Those Initially Tuberculin Positive

Whereas the tuberculin-negative unvaccinated, and the two vaccinated, groups are alike, apart from the vaccination (by virtue of the random allocation process), the two initially tuberculin-positive groups are not. These groups differed on entry not only from those initially tuberculin negative, in the fact of sensitivity to tuberculin, but also from each other, in the degree of this sensitivity. Moreover, the interpretation of any differences in the incidence of tuberculosis between these groups must take into account the differing backgrounds which have led up to the specific differences in sensitivity. Among 15,800 participants with a positive reaction to 3 T.U. (tuberculin units) on entry, the annual incidence of tuberculosis during the first two and a half years was 1.75 per 1,000 participants. Among the 6,500 participants initially negative to 3 T.U. and positive to 100 T.U. who were admitted concurrently with them, the annual incidence was much lower, being 0.74 per 1,000. Thus, as a group, those initially positive only to 100 T.U. were less likely to contract tuberculosis than those positive to 3 T.U. Positive tuberculin reactions at the two levels clearly have different implications. Moreover, the incidence of tuberculosis within the group positive to 3 T.U. was associated with the intensity of the initial reaction to tuberculin. For those with reactions of 5–14 mm. induration to 3 T.U. initially the annual incidence was 0.78 per 1,000, almost the same as for those initially positive only to 100 T.U., but for those with larger reactions to 3 T.U. the incidence was 2.93 per 1,000 (which is higher even than that in the negative unvaccinated group).

It has been suggested (Edwards and Palmer, 1953; Palmer, 1953; World Health Organization Tuberculosis Research Office, 1955) that nearly all the reactions which occur only to a high concentration of tuberculin indicate a non-tuberculous allergy. If, in the present trial, they were *all* non-specific, the incidence of tuberculosis among those positive only to 100 T.U. and that in the negative unvaccinated group might be expected to be similar (unless the non-tuberculous allergy is associated with some protection against tuberculosis). Actually the annual rates differ considerably, being 0.74 per 1,000 for those initially positive only to 100 T.U. and 1.94 per 1,000 for those in the negative unvaccinated group. Indeed, the experience of the group positive only to 100 T.U. is closer to that of the vaccinated groups than to that of the negative unvaccinated group. The interpretation of tuberculin reactions, in relation both to the subsequent development of tuberculosis and to resistance to the disease, requires much more investigation; it is hoped that further information from the present trial may become available for a later report.

Assessment of the Benefits of Vaccination

According to the present results, if *none* of the tuberculin-negative entrants had been vaccinated, 165 cases of tuberculosis would have been expected among them within thirty months of entry. If *all* of them had received B.C.G. vaccine, 30 cases would have been expected. The difference of 135 cases represents a reduction of 82% in the incidence of tuberculosis *in the tuberculin-negative group.*

However, many of the children entering the trial were already tuberculin positive and were thus ineligible for vaccination; the incidence of tuberculosis in this group would not be directly affected by vaccination. It follows that the reduction to be expected in the incidence of tuberculosis in a population group similar to that of the present trial, as a result of vaccinating all the negative reactors to tuberculin, would be substantially less than the 82% expected in the tuberculin-negative group only. In the present trial, taking the 81 cases among the tuberculin-positive entrants into consideration, the expected reduction in the total number of cases within thirty months of entry would have been from 246 (165 plus 81) to 111 (30 plus 81). The difference of 135 cases thus represents an expected reduction of 55% in the incidence of tuberculosis in the tuberculin-negative and tuberculin-positive groups combined.

This estimate, however, has been calculated after the exclusion of 134 previously unsuspected cases of definite tuberculosis which were present on entry to the trial and were nearly all detected as a result of the initial radiographic examination at school (70 excluded at the time of entry, plus 64 subsequently excluded by the assessor; see above). If the preliminary radiograph had not been taken, many of these 134 cases would apparently have arisen after, and within thirty months of, entry to the trial, and would have increased the total cases among those initially tuberculin positive from 81 to a figure of the order of 200. The apparent reduction in the incidence of tuberculosis in the thirty months, as a result of giving B.C.G. vaccine to all those initially tuberculin negative, would in the absence of an initial radiograph have been of the order of 35% (that is, from 165 plus 200 to 30 plus 200), considerably less than the 55% estimated above. As a corollary, in any scheme of vaccination in adolescence, the radiographic examination and follow-up of those found at the outset to be tuberculin positive, particularly those with strong reactions, should be considered.

The benefit to be expected from B.C.G. vaccination may also be expressed in terms of the administrative action required. The expected reduction of 135 cases in the first thirty months would have resulted from the tuberculin testing of 56,000 schoolchildren and the B.C.G. vaccination of the 33,700 with negative reactions to tuberculin. This corresponds to the prevention of 1.6 cases annually (for a period of two and a half years) among every 1,000 children given B.C.G. vaccine, or the prevention of 1.0 cases of tuberculosis annually (for two and a half years) for every 1,000 children given tuberculin tests preparatory to vaccination. The expected effects of using vole bacillus vaccine in place of B.C.G. vaccine would be very similar.

In considering the implications of these findings it should be borne in mind that in the present trial the participants were vaccinated towards the end of their fifteenth year, by which time 40% were tuberculin positive. The

substantial number of previously unsuspected cases of tuberculosis which were present on entry, coupled with the subsequent incidence among the entrants with positive reactions to tuberculin, indicate that it might be desirable to vaccinate schoolchildren before so large a proportion of them had been infected naturally. Until there has been a longer period of follow-up, however, it will not be possible to know whether the protection afforded by the vaccines persists throughout the period of risk in adolescence, although the supplementary results suggest that the substantial protection during the first two and a half years is maintained up to four years after vaccination. In November, 1953, the Ministry of Health introduced an adoptive scheme for the B.C.G. vaccination of tuberculin-negative schoolchildren approaching their fourteenth birthday. In the light of present results, this is a valuable measure. However, not until further information becomes available on the duration of protection afforded by vaccination, and this is considered in relation to the proportions of schoolchildren who are tuberculin positive at different ages, will it be possible to judge the optimum age at which to institute a scheme for a single vaccination of adolescents.

Finally, it should be borne in mind that the cases discovered in the group tuberculin negative on entry and remaining unvaccinated are manifestations of tuberculosis appearing within a few years of a natural first infection with the tubercle bacillus, and that the protection shown to have been afforded by the vaccines concerns these manifestations. The investigation provides no information about the development of tuberculosis in the vaccinated participants during later life.

The trial is still in progress, and the present report is an interim communication. Later reports will contain more detailed analyses over longer periods of time.

VI. SUMMARY

A controlled clinical trial of B.C.G. and vole bacillus vaccines in the prevention of tuberculosis in adolescent boys and girls started in September, 1950. By December, 1952, approximately 56,700 volunteers, all in their final year at secondary modern schools in or near North London, Birmingham, and Manchester, had been included; nearly all were aged between 14½ and 15 years. Those found at an initial radiographic examination to be suffering from tuberculosis, and those known to have been in recent contact with a case of pulmonary tuberculosis at home, were excluded from the trial. This first report presents preliminary results after each participant had been in the trial for two and a half years, with supplementary incomplete information up to four years.

At the initial examination, each entrant had a chest radiograph and an intracutaneous test with 3 T.U. (tuberculin units); those with negative reactions to 3 T.U. were tested with 100 T.U. Those negative to both strengths were allocated by a random process to an unvaccinated, a B.C.G.-vaccinated, or a vole-bacillus-vaccinated group. The participants were thus automatically classified on entry into the following five groups: tuberculin negative, left unvaccinated (13,300 entrants); tuberculin negative, B.C.G. vaccinated (14,100); tuberculin negative, vole bacillus vaccinated (6,700); tuberculin positive to 3 T.U. (16,000); and tuberculin positive to 100 T.U. but not to 3 T.U. (6,600). Vole bacillus vaccine was not used in the London area, and was not available for all of the time in the Birmingham and Manchester areas. Many of the volunteers had a second examination (similar to the first) three to five months after entry, while they were still at school. No participant was vaccinated or revaccinated by the investigating teams subsequent to the examination on entry.

After leaving school, participants in each of the five groups have been followed with similar intensity by means of a fourteen-month cycle of inquiry and examination, each cycle consisting of a postal inquiry, a home visit by a health visitor, and an examination which, as before, included a chest radiograph and tuberculin tests. As a result, contact was made with 94% of the participants by at least one of these three means within eighteen months of entry; information has since been obtained from many of the remaining 6%. In addition to these methods of discovering the cases of tuberculosis which arose, information from notification lists of medical officers of health and from chest clinic records was also made available.

All definite and suspected cases of tuberculosis have been reviewed and classified by an independent assessor, who, to avoid bias, was kept unaware both of the results of all the tuberculin tests and of whether any vaccination had been performed. A total of 165 definite cases began within two and a half years of entry to the trial. Of these, 63% were of pulmonary tuberculosis and 22% of pleural effusion without evidence of pulmonary tuberculosis; 68% of the cases were severe enough for the patients to be taken off work for at least three months. There was no death from the disease during the two and a half years.

The annual incidence of tuberculosis in the tuberculin-negative unvaccinated group was 1.94 per 1,000; in the B.C.G.-vaccinated group it was only 0.37 per 1,000; and in the vole-bacillus-vaccinated group only 0.44 per 1,000. (Strictly this last figure should be compared with the incidence among those participants in the Birmingham and Manchester areas who were admitted concurrently with those given vole bacillus vaccine—namely, with 2.06 per 1,000 in the negative unvaccinated group and 0.31 per 1,000 in the B.C.G.-vaccinated group.) Each vaccine therefore conferred a substantial and similar degree of protection against tuberculosis over a period of two and a half years in adolescence. The strength of the earlier batches of vole bacillus vaccine was below the standard intended.

The protection conferred by each vaccine was evident soon after it had been given, and was still substantial between two and two and a half years after entry. Supplementary incomplete information up to four years suggests that the protection is maintained for this period. Although the numbers of cases in the vaccinated groups were small, the evidence does not indicate that protection was limited to tuberculosis in particular sites, nor that the pulmonary lesions were less extensive or severe in those who had been vaccinated but developed the disease.

Complications of vaccination consisted of occasional regional adenitis and delayed healing of the local lesion. Two cases of erythema nodosum were also attributed to B.C.G. vaccine. In addition, a number of those given vole bacillus vaccine developed lesions, indistinguishable from lupus vulgaris, at the site of vaccination; up to the end of June, 1955, 22 of these had required treatment.

Among the entrants with a positive reaction to 3 T.U. the annual incidence of tuberculosis was 1.75 per 1,000, compared with 0.74 per 1,000 among those positive only to 100 T.U. The annual incidence was particularly high

among those with strong reactions to 3 T.U. on entry (15 mm. induration or more)—namely, 2.93 per 1,000, compared with 0.78 per 1,000 among those with 5–14 mm. induration. Thus, in this age group those highly sensitive to tuberculin appear to have a special risk of developing tuberculosis.

The annual incidence of 0.74 per 1,000 among those positive only to 100 T.U. compares with 1.94 per 1,000 in the concurrent negative unvaccinated group. These results are not those which would be expected if positive reactions to 100 T.U. only were non-specific for tuberculous infection. The interpretation of weak reactions to tuberculin requires further investigation.

If no participant in the present trial had been vaccinated, a total of 246 cases of tuberculosis would have been expected within two and a half years of entry; if all the tuberculin-negative entrants had received B.C.G. vaccine a total of 111 would have been expected. This represents an expected reduction of 55% in the total incidence of tuberculosis for the two and a half years. However, 134 cases of previously unsuspected definite tuberculosis which were present on entry were excluded from the trial, nearly all as a result of the initial radiographic examination. In the absence of this radiograph, many of these cases would apparently have arisen after entry, and the apparent reduction in the total incidence of tuberculosis would have been only of the order of 35%.

The implications of these interim findings for the use of vaccination in the control of tuberculosis in adolescents are discussed. The trial is still in progress, and later reports will contain more detailed analyses over longer periods of time.

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In addition to those named, many other medical officers of health and chest physicians in all parts of the United Kingdom arranged visits and examinations for participants who moved into their areas. National and local health authorities in the following countries have given similar assistance; Australia, Belgium, Bermuda, Canada, France, Germany, the Gold Coast, Holland, Kenya, Malaya, Malta, New Zealand, Portugal, the Rhodesias, Switzerland, Tanganyika, Tangier, Trinidad, the Union of South Africa, and nineteen of the United States of America.

The Committee regrets that it is impossible to name individually the large number of health visitors and school nurses who are making a vital contribution to the trial by repeated visiting of the participants, as an addition to their normal duties; without their devoted work this investigation could not have continued.

The Ministry of Education assisted in the launching of this investigation; the intake made considerable administrative demands upon the head teachers and staffs of the secondary modern schools in the areas, and they were most helpful and co-operative throughout. The mobile vans for miniature radiography were lent by the Ministry of Health and maintained by the Ministry of Works, the van in the London area being provided by the North-west Metropolitan Regional Hospital Board. Mass radiography units in many of the areas, and the Slough Industrial Health Service, co-operated by arranging for extra radiographic examinations of participants. The medical authorities of the Army, the Royal Navy, the Royal Air Force, and the Merchant Navy are co-operating in the follow-up of participants who enter these Services. The Institute of Child Health of Birmingham University has provided part-time clerical assistance. The National Association for the Prevention of Tuberculosis helped in providing publicity material.

The following also assisted locally in various ways in maintaining contact with the participants: Women's Voluntary Services; the Order of Red Cross and St. John; industrial medical officers; youth employment officers; chambers of commerce; a large number of employers; the public relations officer of Middlesex County Council; cinema circuits; leaders of youth clubs.

The Committee wishes to thank all these, and the many other individuals and organizations which are assisting in the investigation.

Finally, the Committee thanks the secretarial and technical staff of the Tuberculosis Research Unit for their unstinting efforts and the contributions they have made to the smooth running of the trial.

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Two new research reactors (or atomic piles) are operating at Harwell. They are Zeus, a name adopted from the initials of its title "zero energy uranium system," and Zetr ("zero energy thermal reactor"). Zeus has been built to check the nuclear calculations on which the design of the fast reactor being built at Dounreay in the north of Scotland depends, and in many essentials it is a full-scale model of the Dounreay reactor. The cylindrical core of the reactor, which is roughly 20 in. in diameter and 20 in. long, is made up of uranium; this uranium is very highly enriched in the rare uranium 235 isotope. Thus in Zeus uranium is used as a fuel, whereas in Zephyr, the first fast reactor at Harwell, plutonium is the fuel. The core of Zeus is surrounded by many tons of uranium, in which plutonium is formed gradually as the pile runs. The amount of uranium 235 needed to permit the nuclear reaction to start was found to be very close to the predicted value. Zetr uses a nuclear fuel in solution and is intended to provide information about the quantities of fuel which will be required for large-scale reactors using such solutions. Plutonium has already been studied in this reactor; uranium 235 is being studied now; and uranium 233 is to be studied later this year. Natural water is used as a solvent at present, but in the summer heavy water is to be used. Other reactors operating at Harwell are "Gleep" (graphite low energy experimental pile) and "Bepo" (British experimental pile), in which the fuel is natural uranium rods in graphite; "Zephyr" (zero energy fast reactor) with plutonium as fuel, in which it has been shown that two atoms of fissile material can be created for each one burned; and "Dimple" (deuterium moderated pile low energy), in which the fuel is contained in heavy water. In addition there are three other reactors under construction: "Dido" and "Pluto," both powerful research tools in which the fuel is contained in heavy water, and "Lido," a "swimming-pool" type of reactor in which the fuel elements are in a tank of ordinary water.